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Docket No.: PF-0526 USN

Response Under 37 C.F.R. 1.116 - Expedited Procedure

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Tang et al.

Title: HUMAN TRANSMEMBRANE PROTEINS

Serial No.: 09/700,590 Filing Date: April 16, 2001

Examiner: Seharaseyon, J. Group Art Unit: 1647

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TRANSMITTAL FEE SHEET

Sir:

Transmitted herewith are the following for the above-identified application:

1. Return Receipt Postcard; and
2. Brief on Appeal, including Appendix (59 pp., in triplicate).

The fee has been calculated as shown below.

Claims	Claims After Amendment		Claims Previously Paid For		Present Extra	Other Than Small Entity Rate	Fee		Additional Fee(s)
Total	10		20			x$18.00		$	0
Indept.	2		3			x$86.00		$	0
First Presentation of Multiple Dependent Claims						+290.00		$	0
							Total Fee:	$	0

X Fee for filing a Brief in support of an Appeal under 37 CFR 1.17(c): $ 330.00

X Please charge Deposit Account No. **09-0108** in the amount of : $ 330.00

The Commissioner is hereby authorized to charge any additional fees required under 37 CFR 1.16 and 1.17, or credit overpayment to Deposit Account No. 09-0108. **A duplicate copy of this sheet is enclosed.**

Respectfully submitted,

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By: _____ Printed: ~~Annette Parker~~ Jeannie G. Labra

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Tang et al.

Title:	HUMAN TRANSMEMBRANE PROTEINS		
Serial No.:	09/700,590	Filing Date:	April 16, 2001
Examiner:	Seharaseyon, J.	Group Art Unit:	1647

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed **February 3, 2004**, and received by the USPTO on **February 5, 2004**, herewith are three copies of Appellants' Brief on Appeal. Authorized fees include the $ **330.00** fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims **23-29 and 31** of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to **Incyte Genomics, Inc., (now Incyte Corporation)** (Reel 011724, Frame 0727) which is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 23-29 and 31
Claims allowed:	(none)
Claims canceled:	Claims 1-20
Claims withdrawn:	Claims 21, 22, 30, and 32-40
Claims on Appeal:	Claims 23-29 and 31 (A copy of the claims on appeal can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

There were no amendments submitted after Final Rejection.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to a polynucleotide sequence corresponding to a gene that is expressed in humans. The novel polynucleotide codes for a polypeptide (HTMPN-22) demonstrated in the patent specification to be a member of the class of Ring3-related bromodomain proteins, whose biological functions include regulation of transcription and cell growth. HTMPN-22 was identified as a Ring3 homolog in column 6 of Table 2 (see page 79 of the specification). HTMPN-22 also contains a bromodomain, a domain found in various transcriptional regulators, at residues A80-N140, which is shown as a signature sequence in column 5 of Table 2 (specification, page 79). Moreover, northern analysis of SEQ ID NO:101 shows its expression predominantly in cDNA libraries associated with cancer, inflammation and the immune response, and fetal development (specification, Table 3 at page 88). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide

coded for by the polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

(6) ISSUES

1. Whether claims 23-29 and 31 directed to HTMPN-22 encoding polynucleotide sequences meet the utility requirement of 35 U.S.C. §101.

2. Whether one of ordinary skill in the art would know how to use the claimed sequences, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

3. Whether the polynucleotides encoding variants and fragments of HTMPN-22 as recited in claims 23, 26-28, and 31 are unpatentable under 35 U.S.C. §112, first paragraph, for reason that the specification does not enable one of ordinary skill in the art to make and use the claimed sequences.

4. Whether the polynucleotides encoding variants and fragments of HTMPN-22 as recited in claims 23, 26-28, and 31 are unpatentable under 35 U.S.C. §112, first paragraph, for reason that the invention is not described in the specification and/or particularly pointed out by the claims.

(7) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

All of the claims on appeal are grouped together.

As to Issue 3

This issue pertains only to claims 23, 26-28, and 31, as the other claims on appeal do not recite variants or fragments of SEQ ID NO:22 or SEQ ID NO:101 (see the Advisory Action mailed March 23, 2004, page 3).

As to Issue 4

This issue pertains only to claims 23, 26-28, and 31, as the other claims on appeal do not recite variants or fragments of SEQ ID NO:22 or SEQ ID NO:101 (see the Advisory Action mailed March 23, 2004, page 3).

(8) APPELLANTS' ARGUMENTS

ISSUES ONE AND TWO: Claims 23-29 and 31 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that: "Since neither the prior art nor the specification provides for the physiological significance of the disclosed and claimed novel polynucleotides encoding the proteins, there is no immediately obvious patentable use for it. In addition, the instant specification does not not disclose a "real world" use for said polynucleotides, except the prophetic recitation of potential uses, which include possible biological and therapeutic uses. Also, there are no working examples that demonstrate any specific utility. Thus, the claimed invention is incomplete, and therefore, does not meet the requirements of 35 U.S.C. 101 as being useful. Therefore the polynucleotides of the invention are not supported by a specific and substantial utility or a well-established utility" (Office Action mailed March 25, 2003, pages 5-6).

The rejection of claims 23-29 and 31 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The invention at issue is a polynucleotide sequence corresponding to a gene that is expressed in humans. The novel polynucleotide codes for a polypeptide (HTMPN-22) demonstrated in the patent specification to be a member of the class of Ring3-related bromodomain proteins, whose biological functions include regulation of transcription and cell growth. HTMPN-22 was identified as a Ring3 homolog in column 6 of Table 2 (see page 79 of the specification). HTMPN-22 also contains a bromodomain, a domain found in various transcriptional regulators, at residues A80-N140, which is shown as a signature sequence in column 5 of Table 2 (specification, page 79). Moreover, northern analysis of SEQ ID NO:101 shows its expression predominantly in cDNA libraries associated with

cancer, inflammation and the immune response, and fetal development (specification at page 88). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Appellants have previously submitted (with the Response to Office Action filed June 24, 2003) the First Declaration of Bedilion describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The First Bedilion Declaration demonstrates that the positions and arguments made by the Examiner with respect to the utility of the claimed polynucleotide are without merit.

Appellants note that the instant application is the National Stage of International Application No. PCT/US99/11904, filed May 28, 1999, which claims the benefit under 35 U.S.C. § 119(e) of provisional application U.S. Ser. No. 60/087,260, filed May 29, 1998 (hereinafter the Tang '260 application). The Tang '260 application contains the same disclosure with respect to the claimed invention as the Tang '590 application. For the sake of convenience, Appellants cite to and discuss the Tang '590 specification below on the understanding that the descriptions in that specification have the May 29, 1998 priority date of the Tang '260 application.

The First Bedilion Declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would [have appreciated on May 29, 1998] that cDNA microarrays that contained the SEQ ID NO:22-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cell proliferative and immune disorders for such purposes as evaluating their efficacy and toxicity. (First Bedilion Declaration, ¶ 15.

The Final Office Action included arguments made and positions taken for the first time in a misplaced attempt to justify the rejections of the claims under 35 U.S.C. §§ 101 and 112. This is particularly so with respect to the specific, substantial, and credible utilities disclosed in the Tang '260 application (to which the instant application claims priority) relating to the use of the SEQ ID NO:22-encoding polynucleotides for gene expression monitoring applications. Such gene expression monitoring applications are highly useful in drug development and in toxicity testing.

The Final Office Action's new positions and arguments included that (a) the use of the claimed polynucleotides in monitoring gene expression is "not specific" (Final Office Action, e.g., pages 7-8); and (b) the gene expression monitoring results obtained using the claimed SEQ ID NO:22-encoding polynucleotides are allegedly "not ... informative" or otherwise insufficient to constitute substantial, specific and credible utilities for the SEQ ID NO:1 polypeptide (Final Office Action, e.g., page 5). The Final Office Action further asserted that the previously submitted references describing gene expression profiling, such as Rockett et al., and Lashkari et al. allegedly support the Examiner's assertion that "the use of the claimed polynucleotides in either microarrays or gene expression monitoring merely constitutes further research to determine the significance of the claimed nucleic acid itself" (Final Office Action, page 9).

Under the circumstances, Applicants submitted with the Response to Final Office Action filed February 3, 2004, the Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with attached Exhibits A - Q; the Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E; the Second Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132; and ten (10) references published before the May 29, 1998 priority date of the instant application. As shown in the Response to Office Action filed February 3, 2004 and in this Appeal Brief, the Rockett Declaration, the Iyer Declaration, the Second Bedilion Declaration, and the accompanying references show the many substantial reasons why the Final Office Actions's new positions and arguments with respect to the use of the claimed SEQ ID NO:22-encoding polynucleotides in gene expression monitoring applications are without merit.

The fact that the Rockett, Iyer, and Second Bedilion Declarations, along with the accompanying references, were submitted in response to positions taken and arguments made for the

first time in the Final Office Action, including arguments disregarding the persuasiveness of the First Bedilion Declaration, constitutes by itself "good and sufficient reasons" under 37 C.F.R. § 1.195 why these Declarations and references were not earlier submitted and should be admitted at this time. Appellants also note that the submitted Declarations and references are responsive to the new utility rejection as framed by the Board of Appeals in copending cases with similar issues.

The Rockett Declaration, Iyer Declaration, Second Bedilion Declaration, and the ten (10) references fully establish that, prior to the May 29, 1998 filing date of the parent Tang '260 application, it was well-established in the art that:

> polynucleotides derived from nucleic acids expressed in one or more tissues and/or cell types can be used as hybridization probes -- that is, as tools -- to survey for and to measure the presence, the absence, and the amount of expression of their cognate gene;
>
> with sufficient length, at sufficient hybridization stringency, and with sufficient wash stringency -- conditions that can be routinely established -- expressed polynucleotides, used as probes, generate a signal that is specific to the cognate gene, that is, produce a gene-specific expression signal;
>
> expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts, in toxicology, particularly toxicology studies conducted early in drug development efforts, and in phenotypic characterization and categorization of cell types, including neoplastic cell types;
>
> each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;
>
> biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;
>
> nucleic acid microarrays increase the parallelism of expression measurements, providing expression data analogous to that provided by older, lower throughput techniques, but at substantially increased throughput;

accordingly, when expression profiling is performed using microarrays, each additional gene-specific probe that is included as a signaling component on this analytical device increases the detection range, and thus versatility, of this research tool;

biologists, such as toxicologists, recognize the increased utility of such improved tools, and thus want a gene-specific probe to each newly identified expressed gene to be included in such an analytical device;

the industrial suppliers of microarrays recognize the increased utility of such improved tools to their customers, and thus strive to improve salability of their microarrays by adding each newly identified expressed gene to the microarrays they sell;

it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;

failure of a probe to detect changes in expression of its cognate gene does not diminish the usefulness of the probe as a research tool; and

failure of a probe completely to detect its cognate transcript in any single expression analysis experiment does not deprive the probe of usefulness to the community of users who would use it as a research tool.

The Patent Examiner does not dispute that the claimed polynucleotide can be used as a probe in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of the biological function of the protein it encodes. But the law has never required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the First and Second Bedilion Declarations, the Rockett Declaration, and the Iyer Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise function.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Toxicology testing, drug discovery, and disease diagnosis are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the previously submitted First and Second Bedilion Declarations, the Rockett Declaration, and the Iyer Declaration. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of the SEQ ID NO:22-encoding polynucleotides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the previously submitted First and Second Bedilion Declarations, the Rockett Declaration, and the Iyer Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotide.

In his First Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Tang '590 priority application, the Tang '260 application, on May 29, 1998 would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs (First Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotide in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications (First Bedilion Declaration, ¶¶ 12 and 15).[1]

In connection with his explanations, Dr. Bedilion states that the "specification of the Tang '260 application would have led a person skilled in the art in May, 1998 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of cell proliferative and immune disorders [a] to conclude that a cDNA microarray that contained the SEQ ID NO:22-encoding polynucleotides would be a highly useful tool, and [b] to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:22-encoding polynucleotides" (First Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [have appreciated on May 29, 1998] that cDNA microarrays that

[1]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Tang '590 specification, that the claimed polynucleotide would be useful in connection with developing new drugs using technology, such as Northern analysis, that predated by many years the development of the cDNA technology (First Bedilion Declaration, ¶ 16).

contained the SEQ ID NO:22-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cell proliferative and immune disorders for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-May 29, 1998 publications showing the state of the art on May 29, 1998 (First Bedilion Declaration, ¶ ¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his First Declaration include over three pages of text and six subparts (a)-(f), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on May 29, 1998 (and for several years prior to May 29, 1998) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be evaluated in connection with the development of the drug" and how the teachings of the Tang '260 application clearly include using differential gene expression analyses in toxicity studies (First Bedilion Declaration, ¶ 10).

Thus, the First Bedilion Declaration establishes that persons skilled in the art reading the Tang '260 application at the time it was filed "would have wanted their cDNA microarray to have a [SEQ ID NO:22-encoding polynucleotide probe] because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to May 29, 1998" (First Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than sufficient reason to compel the conclusion that the Tang '260 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

Nowhere does the Patent Examiner address the fact that, as described on page 55 of the Tang '590 application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed

polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added)).

Though Appellants need not so prove to demonstrate utility, there can be no reasonable dispute that persons of ordinary skill in the art have numerous uses for information about relative gene expression including, for example, understanding the effects of a potential drug for treating cell proliferative and immune disorders. Because the patent application states explicitly that the claimed polynucleotide is known to be expressed both in normal cells as well as cancerous and immortalized cells (see the Tang '590 application at page 88), and expresses a protein that is a member of a class (Ring3-related bromodomain proteins) known to be associated with diseases such as cell proliferative and immune disorders, there can be no reasonable dispute that a person of ordinary skill in the art could put the claimed invention to such use. In other words, the person of ordinary skill in the art can derive more information about a potential drug candidate for treating cell proliferative or immune disorders or potential toxin with the claimed invention than without it (see the First Bedilion Declaration at, e.g., ¶ 15, subparts (e)-(f)).

The First Bedilion Declaration shows that a number of pre-May 29, 1998 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Tang '590 priority application, the Tang '260 application, was filed (First Bedilion Declaration ¶¶ 10-14; First Bedilion Exhibits A-G). Indeed,

Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, First Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (First Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see First Bedilion Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see First Bedilion Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion in his First Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, 29 Xenobiotica No. 7, 655 (1999) (Reference No. 1 enclosed with the Response to Office Action filed June 24, 2003):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Carcinogenesis 153

(1999) (Reference No. 3 enclosed with the Response to Office Action filed June 24, 2003); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, 112-13 Toxicology Letters 467 (2000) (Reference No. 4 enclosed with the Response to Office Action filed June 24, 2003).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec.681, No. 8 (1999) (Reference No. 5 enclosed with the Response to Office Action filed June 24, 2003). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See the email of record from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 6 enclosed with the Response to Office Action filed June 24, 2003), indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In his Second Declaration, Dr. Bedilion explains why a person of skill in the art in 1998 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications

using cDNA microarrays. (Second Bedilion Declaration, e.g., ¶¶ 4-7.) In his Declaration, Dr. Iyer explains why a person of skill in the art in 1998 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, stating that "[t]o provide maximum versatility as a research tool, the microarray should include – and as a biologist I would want my microarray to include – each newly identified gene as a probe." (Iyer Declaration, ¶ 9.)

Further evidence of the well-established utility of all expressed polypeptides and polynucleotides in toxicology testing is found in U.S. Pat. No. 5,569,588 (Reference No. 5 enclosed with the Response to Office Action filed February 3, 2004) and published PCT applications WO 95/21944, WO 95/20681, and WO 97/13877 (References No. 1, 2, and 7 enclosed with the Response to Office Action filed February 3, 2004).

WO 95/21944 ("Differentially expressed genes in healthy and diseased subjects"), published August 17, 1995, describes the use of microarrays in expression profiling analyses, emphasizing that *patterns* of expression can be used to distinguish healthy tissues from diseased tissues and that *patterns* of expression can additionally be used in drug development and toxicology studies, without knowledge of the biological function of the encoded gene product. In particular, and with emphasis added:

> The present invention involves . . . methods for diagnosing diseases . . . characterized by the presence of [differentially expressed] . . . genes, despite the absence of knowledge about the gene or its function. The methods involve the use of a composition suitable for use in hybridization which consists of a solid surface on which is immobilized at pre-defined regions thereon a plurality of defined oligonucleotide/ polynucleotide sequences for hybridization. Each sequence comprises a fragment of an EST. . . . Differences in hybridization patterns produced through use of this composition and the specified methods enable diagnosis of diseases based on differential expression of genes of unknown function . . . . [abstract]

> The method [of the present invention] involves producing and comparing hybridization patterns formed between samples of expressed mRNA or cDNA polynucleotide sequences . . . and a defined set of oligonucleotide/polynucleotide[] . . . immobilized on a support. Those defined [immobilized] oligonucleotide/polynucleotide sequences are representative of the total expressed genetic component of the cells, tissues, organs or organism as defined by the collection of partial cDNA sequences (ESTs). [page 2]

The present invention meets the unfilled needs in the art by providing methods for the . . . use of gene fragments and genes, even those of unknown full length sequence and unknown function, which are differentially expressed in a healthy animal and in an animal having a specific disease or infection by use of ESTs derived from DNA libraries of healthy and/or diseased/infected animals. [page 4]

Yet another aspect of the invention is that it provides . . . a means for . . . monitoring the efficacy of disease treatment regimes including . . . toxicological effects thereof." [page 4]

It has been appreciated that one or more differentially identified EST or gene-specific oligonucleotide/polynucleotides define a pattern of differentially expressed genes diagnostic of a predisease, disease or infective state. A knowledge of the specific biological function of the EST is not required only that the EST[] identifies a gene or genes whose altered expression is associated reproducibly with the predisease, disease or infectious state. [page 4]

As used herein, the term 'disease' or 'disease state' refers to any condition which deviates from a normal or standardized healthy state in an organism of the same species in terms of differential expression of the organism's genes. . . [whether] of genetic or environmental origin, for example, an inherited disorder such as certain breast cancers. . . .[or] administration of a drug or exposure of the animal to another agent, e.g., nutrition, which affects gene expression. [page 5]

As used herein, the term 'solid support' refers to any known substrate which is useful for the immobilization of large numbers of oligonucleotide/polynucleotide sequences by any available method . . . [and includes, inter alia,] nitrocellulose, . . . glass, silica. . . . [page 6]

By 'EST' or 'Expressed Sequence Tag' is meant a partial DNA or cDNA sequence of about 150 to 500, more preferably about 300, sequential nucleotides. . . . [page 6]

One or more libraries made from a single tissue type typically provide at least about 3000 different (i.e., unique) ESTs and potentially the full complement of all possible ESTs representing all cDNAs e.g., 50,000 - 100,000 in an animal such as a human. [page 7]

The lengths of the defined oligonucleotide/ polynucleotides may be readily increased or decreased as desired or needed. . . . The length is generally guided by the principle that it should be of sufficient length to insure that it is on[] average only represented once in the population to be examined. [page 7]

> Comparing the . . . hybridization patterns permits detection of those defined oligonucleotide/ polynucleotides which are differentially expressed between the healthy control and the disease sample by the presence of differences in the hybridization patterns at pre-defined regions [of the solid support]. [page 13]
>
> It should be appreciated that one does not have to be restricted in using ESTs from a particular tissue from which probe RNA or cDNA is obtained[;] rather any or all ESTs (known or unknown) may be placed on the support. Hybridization will be used [to] form diagnostic patterns or to identify which particular EST is detected. For example, all known ESTs from an organism are used to produce a 'master' solid support to which control sample and disease samples are alternately hybridized. [page 14]
>
> Diagnosis is accomplished by comparing the two hybridization patterns, wherein substantial differences between the first and second hybridization patterns indicate the presence of the selected disease or infection in the animal being tested. Substantially similar first and second hybridization patterns indicate the absence of disease or infection. This[,] like many of the foregoing embodiments[,] may use known or unknown ESTs derived from many libraries. [page 18]
>
> Still another intriguing use of this method is in the area of monitoring the effects of drugs on gene expression, both in laboratories and during clinical trials with animal[s], especially humans. [page 18]

WO 95/20681 ("Comparative Gene Transcript Analysis"), filed in 1994 by Appellants' assignee and published August 3, 1995, has three issued U.S. counterparts: U.S. Pat. Nos. 5,840,484, issued November 24, 1998; 6,114,114, issued September 5, 2000; and 6,303,297, issued October 16, 2001.

The specification describes the use of transcript expression *patterns,* or "images", each comprising multiple pixels of gene-specific information, for diagnosis, for cellular phenotyping, and in toxicology and drug development efforts. The specification describes a plurality of methods for obtaining the requisite expression data -- one of which is microarray hybridization -- and equates the uses of the expression data from these disparate platforms. In particular, and with emphasis added:

> The invention provides a "method and system for quantifying the relative abundance of gene transcripts in a biological specimen. . . . [G]ene transcript imaging can be used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. The invention provides a method for comparing the gene transcript image analysis

from two or more different biological specimens in order to distinguish between the two specimens and identify one or more genes which are differentially expressed between the two specimens." [abstract]

"[W]e see each individual gene product as a 'pixel' of information, which relates to the expression of that, and only that, gene. We teach herein [] methods whereby the individual 'pixels' of gene expression information can be combined into a single gene transcript 'image,' in which each of the individual genes can be visualized simultaneously and allowing relationships between the gene pixels to be easily visualized and understood." [page 2]

"The present invention avoids the drawbacks of the prior art by providing a method to quantify the relative abundance of multiple gene transcripts in a given biological specimen. . . . The method of the instant invention provides for detailed diagnostic comparisons of cell profiles revealing numerous changes in the expression of individual transcripts." [page 6]

"High resolution analysis of gene expression be used directly as a diagnostic profile. . . . " [page 7]

"The method is particularly powerful when more than 100 and preferably more than 1,000 gene transcripts are analyzed." [page 7]

"The invention . . . includes a method of comparing specimens containing gene transcripts." [page 7]

"The final data values from the first specimen and the further identified sequence values from the second specimen are processed to generate ratios of transcript sequences, which indicate the differences in the number of gene transcripts between the two specimens." [i.e., the results yield analogous data to microarrays] [page 8]

"Also disclosed is a method of producing a gene transcript image analysis by first obtaining a mixture of mRNA, from which cDNA copies are made." [page 8]

"In a further embodiment, the relative abundance of the gene transcripts in one cell type or tissue is compared with the relative abundance of gene transcript numbers in a second cell type or tissue in order to identify the differences and similarities." [page 9]

"In essence, the invention is a method and system for quantifying the relative abundance of gene transcripts in a biological specimen. The invention provides a method for comparing the gene transcript image from two or more different biological specimens in order to distinguish between the two specimens. . . . " [page 9]

"[T]wo or more gene transcript images can be compared and used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells." [pages 9 – 10]

"The present invention provides a method to compare the relative abundance of gene transcripts in different biological specimens. . . . This process is denoted herein as gene transcript imaging. The quantitative analysis of the relative abundance for a set of gene transcripts is denoted herein as 'gene transcript image analysis' or 'gene transcript frequency analysis'. The present invention allows one to obtain a profile for gene transcription in any given population of cells or tissue from any type of organism." [page 11]

"The invention has significant advantages in the fields of diagnostics, toxicology and pharmacology, to name a few." [page 12]

"[G]ene transcript sequence abundances are compared against reference database sequence abundances including normal data sets for diseased and healthy patients. The patient has the disease(s) with which the patient's data set most closely correlates." [page 12]

"For example, gene transcript frequency analysis can be used to differentiate normal cells or tissues from diseased cells or tissues. . . ." [page 12]

"In toxicology, . . . [g]ene transcript imaging provides highly detailed information on the cell and tissue environment, some of which would not be obvious in conventional, less detailed screening methods. The gene transcript image is a more powerful method to predict drug toxicity and efficacy. Similar benefits accrue in the use of this tool in pharmacology. . . . " [page 12]

"In an alternative embodiment, comparative gene transcript frequency analysis is used to differentiate between cancer cells which respond to anti-cancer agents and those which do not respond." [page 12]

"In a further embodiment, comparative gene transcript frequency analysis is used . . . for the selection of better pharmacologic animal models." [page 14]

"In a further embodiment, comparative gene transcript frequency analysis is used in a clinical setting to give a highly detailed gene transcript profile of a diseased state or condition." [page 14]

"An alternate method of producing a gene transcript image includes the steps of obtaining a mixture of test mRNA and providing a representative array of unique probes whose sequences are complementary to at least some of the test mRNAs. Next, a fixed

amount of the test mRNA is added to the arrayed probes. The test mRNA is incubated with the probes for a sufficient time to allow hybrids of the test mRNA and probes to form. The mRNA-probe hybrids are detected and the quantity determined." [page 15]

"[T]his research tool provides a way to get new drugs to the public faster and more economically." [page 36]

"In this method, the particular physiologic function of the protein transcript need not be determined to qualify the gene transcript as a clinical marker." [page 38]

"[T]he gene transcript changes noted in the earlier rat toxicity study are carefully evaluated as clinical markers in the followed patients. Changes in the gene transcript image analyses are evaluated as indicators of toxicity by correlation with clinical signs and symptoms and other laboratory results. . . . The . . . analysis highlights any toxicological changes in the treated patients." [page 39]

U.S. Pat. No. 5,569,588 ("Methods for Drug Screening") ("the '588 patent"), issued October 29, 1996, with a priority date of August 1995, describes an expression profiling platform, the "genome reporter matrix", which is different from nucleic acid microarrays. Additionally describing use of nucleic acid microarrays, the '588 patent makes clear that the utility of comparing multidimensional expression datasets is independent of the methods by which such profiles are obtained. The '588 patent speaks clearly to the usefulness of such expression analyses in drug development and toxicology, particularly pointing out that a gene's failure to change in expression level is a useful result. Thus, with emphasis added,

The invention provides "[m]ethods and compositions for modeling the transcriptional responsiveness of an organism to a candidate drug. . . . [The final step of the method comprises] comparing reporter gene product signals for each cell before and after contacting the cell with the candidate drug to obtain a drug response profile which provides a model of the transcriptional responsiveness of said organism to the candidate drug." [abstract]

"The present invention exploits the recent advances in genome science to provide for the rapid screening of large numbers of compounds against a systemic target comprising substantially all targets in a pathway [or] organism." [col. 1]

"The ensemble of reporting cells comprises as comprehensive a collection of transcription regulatory genetic elements as is conveniently available for the targeted organism so as to most accurately model the systemic transcriptional response. Suitable

ensembles generally comprise thousands of individually reporting elements; preferred ensembles are substantially comprehensive, i.e. provide a transcriptional response diversity comparable to that of the target organism. Generally, a substantially comprehensive ensemble requires transcription regulatory genetic elements from at least a majority of the organism's genes, and preferably includes those of all or nearly all of the genes. We term such a substantially comprehensive ensemble a genome reporter matrix." [col. 2]

"Drugs often have side effects that are in part due to the lack of target specificity. . . . [A] genome reporter matrix reveals the spectrum of other genes in the genome also affected by the compound. In considering two different compounds both of which induce the ERG10 reporter, if one compound affects the expression of 5 other reporters and a second compound affects the expression of 50 other reports, the first compound is, a priori, more likely to have fewer side effects." [cols. 2 - 3]

"Furthermore, it is not necessary to know the identity of any of the responding genes." [col. 3]

"[A]ny new compound that induces the same response profile as [a] . . . dominant tubulin mutant would provide a candidate for a taxol-like pharmaceutical." [col. 4]

"The genome reporter matrix offers a simple solution to recognizing new specificities in combinatorial libraries. Specifically, pools of new compounds are tested as mixtures across the matrix. If the pool has any new activity not present in the original lead compound, new genes are affected among the reporters." [col. 4]

" A sufficient number of different recombinant cells are included to provide an ensemble of transcriptional regulatory elements of said organism sufficient to model the transcriptional responsiveness of said organism to a drug. In a preferred embodiment, the matrix is substantially comprehensive for the selected regulatory elements, e.g. essentially all of the gene promoters of the targeted organism are included." [cols. 6 – 7]

"In a preferred embodiment, the basal response profiles are determined. . . . The resultant electrical output signals are stored in a computer memory as genome reporter output signal matrix data structure associating each output signal with the coordinates of the corresponding microtiter plate well and the stimulus or drug. This information is indexed against the matrix to form reference response profiles that are used to determine the response of each reporter to any milieu in which a stimulus may be provided. After establishing a basal response profile for the matrix, each cell is contacted with a candidate drug. The term drug is used loosely to refer to agents which can provoke a specific cellular response. . . . The drug induces a complex response pattern of repression, silence and induction across the matrix . . . .The response profile reflects the

cell's transcriptional adjustments to maintain homeostasis in the presence of the drug. . . . After contacting the cells with the candidate drug, the reporter gene product signals from each of said cells is again measured to determine a stimulated response profile. The basal o[r] background response profile is then compared with . . . the stimulated response profile to identify the cellular response profile to the candidate drug." [cols. 7 – 8]

"In another embodiment of the invention, a matrix [i.e., array] of hybridization probes corresponding to a predetermined population of genes of the selected organism is used to specifically detect changes in gene transcription which result from exposing the selected organism or cells thereof to a candidate drug. In this embodiment, one or more cells derived from the organism is exposed to the candidate drug in vivo or ex vivo under conditions wherein the drug effects a change in gene transcription in the cell to maintain homeostasis. Thereafter, the gene transcripts, primarily mRNA, of the cell or cells is isolated . . . [and] then contacted with an ordered matrix [array] of hybridization probes, each probe being specific for a different one of the transcripts, under conditions where each of the transcripts hybridizes with a corresponding one of the probes to form hybridization pairs. The ordered matrix of probes provides, in aggregate, complements for an ensemble of genes of the organism sufficient to model the transcriptional responsiveness of the organism to a drug. . . . The matrix-wide signal profile of the drug-stimulated cells is then compared with a matrix-wide signal profile of negative control cells to obtain a specific drug response profile." [col. 8]

"The invention also provides means for computer-based qualitative analysis of candidate drugs and unknown compounds. A wide variety of reference response profiles may be generated and used in such analyses." [col. 8]

"Response profiles for an unknown stimulus (e.g. new chemicals, unknown compounds or unknown mixtures) may be analyzed by comparing the new stimulus response profiles with response profiles to known chemical stimuli." [col. 9]

"The response profile of a new chemical stimulus may also be compared to a known genetic response profile for target gene(s)." [col. 9]

The August 11, 1997 press release from the '588 patent's assignee, Acacia Biosciences (now part of Merck) (Reference 8 enclosed with the Response to Office Action filed February 3, 2004), and the September 15, 1997 news report by Glaser, "Strategies for Target Validation Streamline Evaluation of Leads," *Genetic Engineering News* (Reference 9 enclosed with the Response to Office Action filed February 3, 2004), attest the commercial value of the methods and technology described and claimed in the '588 patent.

WO 97/13877 ("Measurement of Gene Expression Profiles in Toxicity Determinations"), published April 17, 1997, describes an expression profiling technology differing somewhat from the use of cDNA microarrays and differing from the genome reporter matrix of the '588 patent; but the use of the data is analogous. As per its title, the reference describes use of expression profiling in toxicity determinations. In particular, and with emphasis added:

> "[T]he invention relates to a method for detecting and monitoring changes in gene expression patterns in in vitro and in vivo systems for determining the toxicity of drug candidates." [Field of the invention]
>
> "An object of the invention is to provide a new approach to toxicity assessment based on an examination of gene expression patterns, or profiles, in in vitro or in vivo test systems." [page 3]
>
> "Another object of the invention is to provide a rapid and reliable method for correlating gene expression with short term and long term toxicity in test animals." [page 3]
>
> "The invention achieves these and other objects by providing a method for massively parallel signature sequencing of genes expressed in one or more selected tissues of an organism exposed to a test compound. An important feature of the invention is the application of novel . . . methodologies that permit the formation of gene expression profiles for selected tissues . . . . Such profiles may be compared with those from tissues of control organisms at single or multiple time points to identify expression patterns predictive of toxicity." [page 3]
>
> "As used herein, the terms 'gene expression profile,' and 'gene expression pattern' which is used equivalently, means a frequency distribution of sequences of portions of cDNA molecules sampled from a population of tag-cDNA conjugates. . .. Preferably, the total number of sequences determined is at least 1000; more preferably, the total number of sequences determined in a gene expression profile is at least ten thousand." [page 7]
>
> "The invention provides a method for determining the toxicity of a compound by analyzing changes in the gene expression profiles in selected tissues of test organisms exposed to the compound. . . . . Gene expression profiles derived from test organisms are compared to gene expression profiles derived from control organisms. . . . " [page 7]

Accordingly, Dr. Rockett concludes in his Declaration that:

> It is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s . . . that disclosure of the sequence of a new gene or protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the gene and/or protein in expression profiling studies in toxicology.[2] [Rockett Declaration, ¶ 18.]

C. Appellants' showing of facts overcomes the Examiner's concern that Appellants' invention lacks "specific utility"

The Examiner has alleged that "applicants have disclosed no features or characteristics of the claimed nucleotides encoding SEQ ID NO:22 or nucleotides of SEQ ID NO:101 that would inform the experimenter as to what the significance of detecting that particular sequence would be" and that the use of the claimed polynucleotides in cDNA microarrays is allegedly "the very definition of a *non-specific utility*" (Office Action mailed November 3, 2003, pages 7-8).

Appellants' submission of additional facts with the Response to Office Action filed February 3, 2004, overcomes this concern. Those facts demonstrate that, far from applying ***regardless*** of the specific properties of the claimed invention, the utility of Appellants' claimed polynucleotides as gene-specific probes ***depends upon*** specific properties of the polynucleotides, that is, their nucleic acid sequences.

"[E]ach probe on . . . [a "high density spotted microarray[]"], with careful design and sufficient length, and with sufficiently stringent hybridization and wash conditions, ***binds specifically*** and with minimal cross-hybridization, to the probe's cognate transcript"[3]; "[e]ach gene included as a probe on a microarray provides ***a signal that is specific to the cognate transcript***, at least to a first approximation."[4] Accordingly, "each additional probe makes an additional transcript newly detectable by the microarray, increasing the detection range, and thus versatility, of this analytical device for gene

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"Use of the words 'it is my opinion' to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony." *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

[3] Declaration of Dr. John C. Rockett, ¶ 10(i), emphasis added.

[4] Declaration of Dr. Vishwanath R. Iyer, ¶ 7 (emphasis added). See the footnote at ¶ 7 for a slightly more "nuanced" view.

expression profiling"[5]; equally, "[e]ach new gene-specific probe added to a microarray thus increases the number of genes detectable by the device, increasing the resolving power of the device."[6]

Although not required for present purposes, it would be appropriate to state on the record here that the specificity of nucleic acid hybridization was well-established far earlier than the development of high density spotted microarrays in 1995, and indeed is the well-established underpinning of many, perhaps most, molecular biological techniques developed over the past 30 - 40 years.

The Examiner has agreed that toxicology testing is "a well-established use of polynucleotides and the polypeptides encoded" (Office Action mailed November 3, 2003, page 10), but has asserted that "this is a utility that is non-specific and would apply to virtually every member of a class of materials, such as proteins or DNA" (Office Action mailed November 3, 2003, page 11). Appellants respectfully point out that it is not the case that all DNA molecules would be useful for toxicology testing, only those polynucleotides which are naturally expressed in humans. A random DNA sequence not found in nature, for example, would lack such utility.

While it is true that all polynucleotides expressed in humans have utility in toxicology testing based on the property of being expressed at some time in development or in the cell life cycle, this basis for utility does not preclude that utility from being specific and substantial. A toxicology test using any particular expressed polypeptide or polynucleotide is dependent on the **identity** of that polypeptide or polynucleotide, not on its biological function or its disease association. The results obtained from using any particular human-expressed polypeptide or polynucleotide in toxicology testing is specific to both the compound being tested and the polypeptide or polynucleotide used in the test. **No two human-expressed polypeptides or polynucleotides are interchangeable for toxicology testing** because the effects on the expression of any two such polypeptides or polynucleotides will differ depending on the identity of the compound tested and the **identities** of the two polypeptides or polynucleotides. It is not necessary to know the biological functions and disease associations of the polypeptides or polynucleotides in order to carry out such toxicology tests. Therefore, at the very least,

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5 Declaration of Dr. John C. Rockett, ¶ 10(ii).

6 Declaration of Dr. Vishwanath R. Iyer, ¶ 7.

the claimed polynucleotides are specific controls for toxicology tests in developing drugs targeted to other polypeptides or polynucleotides, and are clearly useful as such.

D. The Rockett and Lashkari references demonstrate that use of the claimed polynucleotides in expression profiling does not merely constitute further research on the claimed polynucleotides themselves

As discussed in the Response to Office Action filed June 24, 2003, literature reviews published shortly after the filing of the Tang '260 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
>
> * * *
>
> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.
>
> * * *
>
> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis added)

Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, 29 Xenobiotica No. 7, 655 (1999) (Reference No. 1 enclosed with the Response to Office Action filed June 24, 2003).

In a pre-May 29, 1998 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, 94 Proc. Nat. Acad. Sci. 8945 (Aug. 1997) (emphasis added) (Reference No. 2 enclosed with the Response to Office Action filed June 24, 2003).

The Examiner has asserted that the Rockett et al. and Lashkari et al. references submitted with the Response to Office Action filed June 24, 2003 allegedly teach that "the use of the claimed polynucleotides in either microarrays or gene expression monitoring merely constitutes further research to determine the significance of the claimed nucleic acid itself" (Office Action mailed November 3, 2003, page 9).

The Examiner first stated that "these references, e.g, Rockett et al. and Lashkari et al. have not been previously cited or discussed on the record, nor have applicants in any information disclosure statement made them of record" (Office Action mailed November 3, 2003, page 8). Appellants note that the Rockett et al. paper (Xenobiotica, 1999 29:655-691) and the Lashkari et al. paper (Proc. Nat. Acad. Sci. U.S.A., 1997, 94:8945-8947) were submitted with the Response to Office Action filed June 24, 2003, to provide evidence of the utility of the claimed invention in gene expression monitoring for toxicology testing. The Examiner is obliged to consider evidence provided by Appellants in support the patentability of the claims.

> Once a prima facie showing of no specific and substantial credible utility has been properly established, the applicant bears the burden of rebutting it. The applicant can do this by amending the claims, by providing reasoning or arguments, or by **providing evidence in the form of a declaration under 37 CFR 1.132 or a patent or a**

> **printed publication that rebuts the basis or logic of the prima facie showing. If the applicant responds to the prima facie rejection, the Office personnel should review the original disclosure, any evidence relied upon in establishing the prima facie showing, any claim amendments, and any new reasoning or evidence provided by the applicant in support of an asserted specific and substantial credible utility. It is essential for Office personnel to recognize, fully consider and respond to each substantive element of any response to a rejection based on lack of utility.** Only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained. (MPEP, § 2107 II. D., emphasis added.)

The Examiner next alleged that the Rockett et al. (Reference No. 1 cited in the Response filed June 24, 2003) and Lashkari et al. (Reference No. 2 cited in the Response filed June 24, 2003) articles teach that use of a polynucleotide in microarrays is useful only for further characterization of the detected genes and probes themselves (Office Action mailed November 3, 20023, pages 8-10). The Examiner quoted the first sentence of the Rockett et al. abstract: "[a]n important feature of the work of many molecular biologists is identifying which genes are turned on and off in a cell under different environmental conditions or subsequent to xenobiotic challenge. **Such information has many uses, including the deciphering of molecular pathways and facilitating the development of new experimental and diagnostic procedures.**" (Office Action mailed November 3, 2003, page 9, emphasis given in Office Action.) The Examiner reads this sentence narrowly, suggesting that the Rockett et al. article teaches that the **only uses** for cDNA microarrays are for further characterization of the detected genes and probes. However, reading further than the first sentence of the Rockett et al. article's abstract, Appellants respectfully note that the authors expand the possible uses of differential gene expression analysis, stating that:

> Differential gene display provides a coherent platform for building libraries and microchip arrays of 'gene fingerprints' characteristic of known enzyme inducers and xenobiotic toxicants, which may be interrogated subsequently **for the identification and characterization of xenobiotics of unknown biological properties**. (Rockett et al., abstract, page 655, emphasis added.)

Rockett et al. teach that "in the field of chemical-induced toxicity, it is now becoming increasingly obvious that most adverse reactions to drugs and chemicals are the result of multiple gene regulation, some of which are causal and some of which are casually-related to the toxicological

phenomenon *per se*. This observation has led to an upsurge in interest in gene-profiling technologies which differentiate between the control and toxin-treated gene pools in target tissues and is therefore, of value in rationalizing the molecule mechanisms of xenobiotic-induced toxicity (Rockett, page 656). Rockett et al. thus teach that microchip analyses are useful for the "identification and characterization of xenobiotics of unknown biological properties," in addition to those uses in "deciphering of molecular pathways and facilitating the development of new experimental and diagnostic procedures. The Examiner has ignored these teachings in the discussion in the Office Action mailed November 3, 2003.

The Examiner further alleged that the Lashkari et al. article (Reference No. 2 cited in the Response filed June 24, 2003) teaches that "sequences of unknown function or significance are used in such strategies [microarrays] *to learn more about the sequences themselves and the genes they represent*" (Office Action mailed November 3, 2003, page 10, emphasis in original). The Examiner cited several lines from the first page of the Lashkari et al. article. Reading further into the article, Appellants respectfully note that Lashkari et al. teach broader uses for cDNA microarrays that the narrow reading adopted by the Examiner. For example, whole genome analysis is useful because it allows one to "analyze numerous genes under many conditions" (Lashkari et al., page 8946). In addition, Lashkari et al. teach that data from genome projects will not only allow one "to gain a truly comprehensive understanding of gene function" but also "more broadly, of the entire genome" (Lashkari et al., page 8947). Furthermore, such understanding "should come from the viewpoint of the integration of complex regulatory networks, the individual roles and interactions of thousands of functional gene products, and the effect of environmental changes on both gene regulatory networks and the roles of all gene products. The time has come to switch from the analysis of a single gene to the analysis of the whole genome" (Lashkari et al, page 8947). Hence, the Lashkari et al. article supports the utility of open reading frames (ORFs) in whole genome analysis by cDNA microarrays and in particular, for determining the "effect of environmental changes on gene regulatory networks and the roles of all gene products" (Lashkari et al., page 8947).

Furthermore, Appellants have submitted with the Response to Office Action filed February 3, 2004, the Declaration of John C. Rockett, who is the first author of the Rockett paper. Dr. Rockett

himself points out that his article describes how gene expression profiling is useful in toxicology, quoting several pertinent paragraphs (Rockett Declaration, ¶ 15). Dr. Rockett concludes that: "In the context of such *patterns* of gene expression, each additional gene-specific probe provides an additional signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution -- and thus more useful -- pattern than otherwise would have been possible.[7]" (Rockett Declaration, ¶¶ 16-17).

The Iyer Declaration provides additional examples of uses for the claimed nucleotides in microarrays, including toxicology testing and classification of human tumor cell lines (Iyer Declaration, ¶ 5). As Dr. Iyer points out, "each new gene probe added to a microarray increases the usefulness of the device in gene expression profiling analyses" (Iyer Declaration, ¶ 7), by increasing the resolving power of the array. This increased resolution provides results, such as subdivisions of otherwise indistinguishable cancers into a greater number of classes, permitting better individualizing of therapy, that are simply not available with less complete arrays (Iyer Declaration, ¶ 8).

Dr. Iyer explicitly states that "these pattern-based analyses do not require knowledge of the biological function of the encoded proteins" (Iyer Declaration, ¶ 5). Dr. Rockett concurs that "disclosure of the sequence of a new gene or protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the gene and/or protein in expression profiling studies in toxicology" (Rockett Declaration, ¶ 18). Thus there is no need to show that SEQ ID NO:101 has identical expression patterns to a known cancer marker or is a surrogate for a cell protein of interest in toxicology, as asserted by the Examiner (Office Action mailed November 3, 2003, page 16).

For these reasons, the claimed sequences are not analogous to the compounds of *Brenner v Manson*, as the Examiner attempts to argue (Office Action mailed November 3, 2003, page 15). The claimed sequences do not merely have a "substantial likelihood" of being useful, or a good probability of being "*eventually* shown to be useful for *something*" (Office Action mailed November 3, 2003,

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[7] In a sense, each gene-specific probe used in such an analysis is analogous to a different one of the many parts of an engine, with each individual part, or subcombinations of such parts, deriving at least part of their usefulness from the utility of the completed combination, the functioning engine.

pages 14-15). Rather, they are useful **today**, in the real world, for specific, substantial and credible uses in, for example, toxicology testing and discrimination between cancer subtypes.

E. Use of the claimed polynucleotides in toxicology testing

The Examiner has asserted that the First Bedilion Declaration is insufficient to overcome the utility rejection "because the instant specification provides general methods and no specific examples" (Office Action mailed November 3, 2003, page 6). The Examiner further asserted that "no demonstration of the use of specific SEQ IDs for the purpose of detecting differential expression and in the use for diagnosis is provided" (Office Action mailed November 3, 2003, page 7).

These arguments amount to nothing more than the Examiner's disagreement with the First Bedilion Declaration and the Appellants' assertions about the knowledge of a person of ordinary skill in the art, and is tantamount to the substitution of the Examiner's own judgment for that of the Appellants' expert. The Examiner must accept the Appellants' assertions to be true. The Examiner is, moreover, wrong on the facts because the First Bedilion Declaration demonstrates how one of skill in the art, reading the specification at the time the Tang '260 application was filed (May 29, 1998), would have understood that specification to disclose the use of the claimed polynucleotides in gene expression monitoring for toxicology testing, drug development, and the diagnosis of disease (See the First Bedilion Declaration at, e.g., ¶¶ 10-16).

Nowhere does the Examiner address the fact that, as described on page 55 of the Tang '590 application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The specification makes clear that "oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray" (specification, page 55, lines). These described polynucleotide sequences clearly include SEQ ID NO:101 (see the specification, page 12, line 18) and polynucleotides encoding SEQ ID NO:22 (specification, page 12, lines 1-2), polynucleotide variants having at least 90% polynucleotide sequence identity to SEQ ID

NO:101 (specification, page 12, line 32 through page 13, line 2) and polynucleotides having at least 90% identity to polynucleotides encoding SEQ ID NO:22 (specification, page 26, lines 27-30).

The claimed invention is not some random sequence whose value as a probe is speculative or would require further research to determine. For example, monitoring the expression of the SEQ ID NO:22-encoding polynucleotides is a method of testing the toxicology of drug candidates during the drug development process. Dr. Bedilion in his First Declaration states that "good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets" (First Bedilion Declaration ¶ 10). Thus, if the expression of a particular polynucleotide is affected in any way by exposure to a test compound, and if that particular polynucleotide is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound has undesirable toxic side effects. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polynucleotide whose expression is being monitored.

However, the Examiner continues to view the utility in toxicology testing of the claimed polynucleotides as requiring knowledge of either the biological function or disease association of the claimed polynucleotides. The Examiner views toxicology testing as a process to measure the toxicity of a drug candidate only when that drug candidate is specifically targeted to the claimed polynucleotides. The Examiner has refused to consider that the claimed polynucleotides are useful for measuring the toxicity of drug candidates which are targeted not to the claimed polynucleotides, but to **other** polynucleotides. This utility of the claimed polynucleotides does not require any knowledge of the biological function or disease association of the SEQ ID NO:22 polypeptide or SEQ ID NO:101 polynucleotide and is a specific, substantial and credible utility.

F. The similarity of the polypeptide encoded by the claimed invention to another polypeptide of undisputed utility demonstrates utility

In addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, the utility of the claimed polynucleotide can be imputed based on the

relationship between the polypeptide it encodes, HTMPN-22, and another polypeptide of unquestioned utility, Ring3. The two polypeptides have sufficient similarities in their sequences that a person of ordinary skill in the art would recognize more than a reasonable probability that the polypeptide encoded for by the claimed invention has utility similar to Ring3. Appellants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

Appellants have previously submitted the results of a BLAST search performed March 2, 1998 (Exhibit A in the Response to Office Action filed June 24, 2003). The BLAST search demonstrated that HTMPN-22 has 57% homology over 548 amino acid residues to mouse Ring3. HTMPN-22 was therefore identified as a Ring3 homolog in column 6 of Table 2 (see page 79 of the specification). Exhibit B in the Response to Office Action filed June 24, 2003, shows the results of MOTIFS analysis (see the specification at page 107) performed May 7, 1998 that demonstrates the presence of a bromodomain, a domain found in various transcriptional regulators, from residues A80-N140. This region is shown as a signature sequence in column 5 of Table 2 (see page 79 of the specification). Thus the specification identified HTMPN-22 as a Ring3-related bromodomain protein.

Articles published before the May 29, 1998 priority date of the instant application demonstrated that Ring3 was a nuclear serine-threonine kinase responsive to a variety of growth factors including IL-1. See Ocstrowski, J., Florio, S.K., Denis, G.V., Suzuki, H., Bomsztyk, K., "Stimulation of p85/RING3 kinase in multiple organs after systemic administration of mitogens into mice," Oncogene 16:1223-1227 (1998) (Reference No. 7 in the Response to Office Action filed June 24, 2003), page 1223, col. 2. The human RING kinase was known to be very active in leukocytes of patients with acute and chronic leukemias, and "[i]n one leukemic patient in remission the activity of the RING3 kinase in leukocytes returned to normal, suggesting that RING3 kinase may be involved in the pathogenesis of the disease (Ostrowski, page 1223, col. 2). The Ostrowski paper further disclosed that "systemic administration of mitogenic and inflammatory agents into mice stimulates activity of p85/RING3 kinase in a number of organs" (Ostrowski, page 1226, col. 2). The Ostrowski paper concludes that "results of these studies may reflect involvement of p85/RING3 kinase in diseases where abnormal cell proliferation is responsible for the pathological process" which is "consistent with the observation that the activity of this enzyme is very high in leukocytes from patients with acute and

chronic leukemias" (Ostrowski, page 1227, col. 1). Thus at the time of filing one of skill in the art would have understood that HTMPN had significant homology to a Ring3, a protein with a known role in cell proliferative and immune disorders.

Furthermore, northern analysis of SEQ ID NO:101 shows its expression predominantly in cDNA libraries associated with cancer, inflammation and the immune response, and fetal development (specification at page 88). Thus one of skill in the art would have understood at the time of filing that polynucleotides encoding HTMPN-22 would be expected to have utility in the diagnosis of cancers, as described in the specification at, for example, page 53, lines 14-24, or page 54, lines 19-25.

It is undisputed that the polypeptide encoded for by the claimed polynucleotide shares more than 57% sequence identity over 548 amino acid residues with Ring3, a nuclear serine-threonine kinase. In addition, the HTMPN-22 polypeptide contains a bromodomain signature at amino acid residues A80-N140. This is more than enough homology to demonstrate a reasonable probability that the utility of Ring3 can be imputed to the claimed invention (through the polypeptide it encodes). It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et al., "Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA 95:6073-78 (1998) (Reference No. 8 in the Response to Office Action filed June 24, 2003). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the polypeptide encoded for by the claimed polynucleotide is related to Ring3 is, accordingly, very high.

The Examiner must accept the Appellants' demonstration that the homology between the polypeptide encoded for by the claimed invention and Ring3 demonstrates utility by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

Instead, the Examiner has asserted that "the homology of a peptide is not a reliable indicator of the functional characteristics" (Office Action mailed March 25, 2003, page 4). In support of this

assertion, the Office Action cited the paper by Scott et al., although no explanation was provided as to how this paper supports the assertion.

The paper by Scott et al. discloses that the protein pendrin was predicted to be a sulfate transporter based upon sequence homology, but later found to be a transporter of chlorine and iodine instead. Appellants respectfully point out that the closest homolog to pendrin, the DRA protein, transports chloride as well as sulfate (Scott et al., page 441, col. 1). Since pendrin's biological function is believed to be the maintenance of chloride gradients in the inner ear (Scott et al., page 441, col. 2), the homology to DRA is in fact highly related to predictions of pendrin function, if not properly appreciated at the time. This is despite the fact that the degree of homology between pendrin and DRA is only 45%, significantly less than the 57% identity between HTMPN-22 and mouse Ring3. The homology between pendrin and the sulfate transporters was even lower, 29% and 32%. Given the significantly greater degree of homology involved in the current case, one of ordinary skill in the art would be reasonably convinced that HTMPN-22 is indeed a member of the Ring3 related family of bromodomain proteins. In conclusion, the cited reference does not serve to meet the burden of demonstrating that the skilled worker would find it more likely than not that the asserted utility for the claimed protein as a Ring3 related bromodomain protein was not correct. At most, this article stands for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

Furthermore, post-filing art shows that HTMPN-22 has 96% amino acid sequence identity to the short form of human Brd4. As the Office Action mailed March 25, 2003, mentioned, the gene encoding the long form of BRD4 has 99.2% sequence identity to SEQ ID NO:101 (Office Action mailed March 25, 2003, page 11). Appellants note that the Fletcher reference (actually, the French reference, "French, C.A., Miyoshi, I., Aster, J.C., Kubonishi, I., Kroll, T.G., Dal Cin, P., Vargas, S.O., Perez-Atayde, A.R., Fletcher, J.A., *BRD4* bromodomain gene rearrangement in aggressive carcinoma with translocation t(15;19)," Am. J. Pathol. 159:1987-1992 (2001) (Reference No. 9, enclosed with the Response to Office Action filed June 24, 2003) made of record in the Office Action mailed March 25, 2003, is not prior art, as it has a publication date of December, 2001. The French reference discloses that rearrangements of the BRD4 gene are responsible for a particularly aggressive

pediatric carcinoma. The French reference further discloses that the short isoform of BRD4 may inhibit BRD4 long isoform function, thus playing a role in the oncogenic mechanism of BRD4 function (French, page 1991, col. 1). An additional postfiling reference (Maruyama, T., Farina, A., Dey, A., Cheong, J., Bermudez, V.P., Tamura, T., Sciortino, S., Shuman, J., Hurwitz, J., Ozato, K., "A mammalian bromodomain protein, Brd4, interacts with replication factor C and inhibits progression to S phase," Mol. Cell. Biol. 22:6509-6520 (2002) (Reference No. 10, enclosed with the Response to Office Action filed June 24, 2003)) discloses that Brd4 is a member of the BET family of bromodomain proteins which includes Ring3, or Brd2 (Maruyama, page 6509) and that Brd4 regulates cell cycle progression. The French and Maruyama articles thus confirm the identification of HTMPN-22 as a Ring3 related bromodomain protein, and also confirm the association of this sequence with cancers. One of skill in the art would clearly understand that the claimed sequences encoding HTMPN-22, as well as the claimed 90% variants of these sequences, would have utility in the diagnosis of cancer.

The Examiner has acknowledged that the Ocstrowski resference teaches a specific utility, based upon the protein's role in leukemias, but asserted that this utility is "not substantial," because the use is allegedly only "speculative" (Office Action mailed November 3, 2003, pages 11-12). Appellants respectfully point out that the association of RING3 with leukemia is not at all speculative, but a matter of fact. The particular biological function of RING3 in causing the disease may not be known, but the correlation of activity levels of RING3 with leukemia is a well-known fact. The Examiner has stated that it is untrue that the Patent Office is requiring a specific biological function for the claimed sequences, stating that "the mere correlation of the presence of the nucleic acid, in a manner that would be found to be credible by a person of ordinary skill in the art, with the presence of a disease or condition would clearly meet the requirements of 35 U.S.C. § 101" (Office Action mailed November 3, 2003, page 6). **Such an association, correlating increased RING3 activity levels with leukemia and decreased levels with remission of the disease, is precisely what is taught in the Ocstrowski paper**.

The Examiner does not dispute that HTMPN-22 is a member of the Ring3 family, but asserts that membership in a gene family is not enough, absent a specific, substantial and credible utility (Office Action mailed November 3, 2003, page 12). This assertion appears to miss the point -- the fact that

HTMPN-22 is a member of the Ring3 family demonstrates utility because **all** the members of this particular family have utility for the diagnosis of cell proliferative disorders. In fact, the Examiner acknowledges that postfiling art (the French and Maruyama references) confirms that other members of the family, such as BRD4, are also associated with cancers (Office Action mailed November 3, 2003, page 13). In fact, the French reference discloses that the long form of BRD4 is almost identical to SEQ ID NO:101 (99.2% sequence identity). One of skill in the art would clearly understand that the claimed sequences encoding HTMPN-22, as well as the claimed 90% variants of these sequences, would have utility in the diagnosis of cancer.

The Examiner has further asserted that the specification does not recite that HTMPN-22 is specifically involved either in cancer or the diagnosis of cancer (Office Action mailed November 3, 2003, page 13). As discussed above, one of skill in the art would readily understand, based upon the disclosure in the specification identifying HTMPN-22 as a RING3-related bromodomain protein, that HTMPN-22 would be associated with cancer and therefore useful in the diagnosis of cancer. In addition, the specification does disclose that HTMPN-22 is specifically associated with cancer. For example, northern analysis of SEQ ID NO:101 shows its expression predominantly in cDNA libraries associated with cancer, inflammation and the immune response, and fetal development (see Table 3, specification at page 88). Moreover, sequences encoding SEQ ID NO:22 were initially isolated from a brain tumor library (Table 4, specification at page 97). Thus one of skill in the art would have understood at the time of filing that polynucleotides encoding HTMPN-22 would be expected to have utility in the diagnosis of cancers, as described in the specification at, for example, page 53, lines 14-24, or page 54, lines 19-25. One of skill in the art would immediately understand that the fact that these particular lines recite the HTMPN molecules as a group rather than listing them all individually does not mean that the utility described does not apply to each of the HTMPN molecules (including HTMPN-22) individually, as well as to the group as a whole.

G. The asserted utility in toxicology testing and expression profiling also applies to the claimed polynucleotide variants.

The Examiner has stated that the asserted utility for the claimed polynucleotides in toxicology testing and expression profiling would only apply to the exact, naturally occurring sequence and not to nucleic acids which vary by codon degeneracy or to nucleic acids having at least 90% identity to the exact sequence (Office Action mailed November 3, 2003, pages 4-5). Appellants respectfully point out that nucleic acids which vary by codon degeneracy from SEQ ID NO:101 will still encode the amino acid sequence of SEQ ID NO:22. As described in the Rockett Declaration (¶¶ 11-14, and attached Exhibits L-Q), naturally occurring protein sequences such as SEQ ID NO:22 are also useful in expression profiling and toxicology testing. Thus any sequence which encodes SEQ ID NO:22 is useful for the production of SEQ ID NO:22 for use in such applications. Appellants further note that the recited variants of SEQ ID NO:101 are all naturally occurring, and thus share the same utilities as other naturally occurring polynucleotides such as SEQ ID NO:101 in expression profiling and toxicology testing. For this reason, it does not matter if they do not specifically recognize SEQ ID NO:101, since they will recognize their own complementary nucleic acids.

H. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.)

The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. Page et al., in discussing the identification and assignment of candidate targets, states that "rapid identification and assignment of candidate targets and markers represents a huge challenge . . . [t]he process of annotation is similarly aided by the quality and richness of the sequence specific databases that are currently available, both in the public domain and in the private sector (e.g. those supplied by Incyte Pharmaceuticals)" (Page, M.J., Amess, B., Rohlff, C., Stubberfield, C., Parekh, R., "Proteomics: a major new technology for the drug discovery process," Drug Discov. Today 4:55-62 (1999) (Reference No. 11, enclosed with the Response to Office Action filed June 24, 2003) see page 58, col. 2). As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polynucleotide and its use of that polynucleotide on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The

implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

III. The Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not "specific, substantial, and credible" utilities. The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Role Or Function Of An Expressed Polynucleotide Is Not Required To Demonstrate Utility

The Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific (Office Action mailed March 25, 2003, page 4). According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are

not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the First Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15, First Bedilion Declaration), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Because the uses of polynucleotides encoding HTMPN-22 in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. (First Bedilion Declaration at ¶ 15.)

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include utilities in disease diagnosis (pages 51-53), monitoring HTMPN-22 levels during therapeutic intervention (page 50, lines 17-23), genomic mapping (pages 55-56), and in microarrays used to identify genetic variants, mutations, and polymorphisms, and for disease diagnosis and development and testing of therapeutic agents (see the specification at, for example, page 55, lines 9-15).

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. See *supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.

V. To the Extent the Rejection of the Patented Invention under 35 U.S.C. § 112, First Paragraph, Is Based on the Improper Rejection for Lack of Utility under 35 U.S.C. § 101, it Must Be Reversed.

The rejection set forth in the Final Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

ISSUE THREE: Enablement rejections under 35 U.S.C. § 112, first paragraph of the recited variant polynucleotides and polynucleotides encoding polypeptide variants and fragments:

Claims 23, 26-28, and 31 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking adequate enablement. In particular, the Examiner has asserted that depending upon the utility, the specification would be found to be enabling for SEQ ID NO:101 or polynucleotides encoding SEQ

ID NO:22, and possibly methods of making the protein of SEQ ID NO:22, but not for the recited polynucleotide variants or the recited polynucleotides encoding variants or fragments of SEQ ID NO:22 (Office Action mailed November 3, 2003, page 27). The Examiner has asserted that the specification "fails to provide any guidance regarding the changes/modifications contemplated" and that "predicting which homologues would retain the functions of the protein is well outside the realm of routine" (Office Action mailed March 25, 2003, pages 9-10).

Appellants respectfully point out that the claims are directed to polynucleotides, not proteins; thus it is the functionality of the claimed polynucleotides, not the proteins encoded by them, that is relevant. Members of the claimed genus of variants may be useful even if they encode proteins that lack activity. As disclosed in the specification, examples of polynucleotide variants include allelic variants, which result in polypeptides whose structure or function may or may not be altered (page 15, lines 22-29). Further examples of polynucleotide variants include splice variants (which may have additional functional domains or lack domains), species variants, or polymorphic variants, such as single nucleotide polymorphisms (SNPs) (page 23, lines 12-23). The specification discloses how to calculate the % identity between two sequences (see the specification at page 19, line 19 through page 20, line 3), allowing one of skill in the art to determine which naturally occurring sequences are encompassed by the claims.

As discussed above regarding the utility rejection, in Section II.G, the specification, along with what is well known in the art, teach that the claimed polynucleotides which comprise naturally occurring variants of SEQ ID NO:101 are useful in toxicology testing and expression profiling. As discussed above, because the claimed variants are naturally occurring, they are useful in toxicology testing and expression profiling whether or not they are able to hybridize to SEQ ID NO:101, since their own complementary RNA sequences are also found in cells.

The specification also discloses further ways to use the claimed polynucleotide variants. For example, variant sequences having at least 50% sequence identity to HTMPN-22 encoding sequences can be used as probes to detect related sequences (page 50, line 32 through page 51, line 1) including HTMPN-22 variants that may be associated with disease states, such as the diseases listed in the specification at page 36, lines 4-13). See the specification at, for example, pages 50-54 for disclosure

of how to use the claimed sequences in diagnostic assays. SNPs may be used to identify particular human populations, or to identify propensities for disease states (page 23, lines 23-25). The variant polynucleotides could also be used in microarrays to identify genetic variants, mutations, and polymorphisms, and for disease diagnosis and development and testing of therapeutic agents (see the specification at, for example, page 55, lines 9-15). Thus one of ordinary skill in the art would know how to used the claimed variants without any undue experimentation.

Regarding the claimed biologically active fragments, the specification discloses a specific signature sequence, corresponding to a bromodomain, at residues A80-N140 (specification, page 79). The Examiner is incorrect in stating that there is no activity ascribed to this fragment (Office Action mailed November 3, 2003, page 27) because the activities of bromodomain proteins were well known in the art at the time of filing. For example, a bromodomain has utility as a chromatin binding domain (see the French reference, page 1991, col. 1). It is known in the art that bromodomains can by themselves interact with acetylated histones, and thus serve as chromatin targeting modules, without requiring additional protein domains (see the Marayuma reference, page 6519, col. 1). Thus no additional experimentation is required to identify the chromatin-targeting region of HTMPN-22.

The Examiner also attempts to question whether the guidance provided in the specification is sufficient to allow one of skill in the art to make immunologically active fragments of SEQ ID NO:22. The selection of immunogenic epitopes, such as regions at the C-terminus or hydrophilic regions, is described in the specification at page 70, lines 2-7. Appellants respectfully direct the Board's attention to the Paul reference of record (Paul, W.E., Fundamental Immunology, Third Edition, Raven Press, New York, (1993), pages 249-251 (Reference No. 11, enclosed with the Response to Office Action filed February 3, 2004)), which demonstrates that the method disclosed in the specification has an extremely high likelihood of success. Paul concurs that "hydrophilicity has been proposed as a second indication of immunogenicity" and that of all 12 proteins tested, "**the most hydrophilic site of each protein was indeed one of the antigenic sites**" (Paul, page 249, col. 2 (emphasis added)). Thus the art confirms that based upon the guidance provided in the specification, one of ordinary skill in the art would be able to make and use immunogenic fragments of SEQ ID NO:22 (or polynucleotides encoding these fragments) without any undue experimentation. The immunologically active fragments

can be used to generate antibodies, which are useful in the diagnostic methods described in the specification at, for example, page 49, line 29 through page 50, line 16, or in the drug screening methods describes in the specification at page 57, lines 2-5. In addition, the use of catalytic or immunogenic fragments in drug screening is disclosed in the specification at page 56, lines 20-25.

Thus one of skill in the art would clearly understand how to both make and use the claimed polynucleotides encoding biologically and immunologically active fragments.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any **reasons** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited polynucleotides. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited polynucleotides.

For at least the above reasons, the enablement rejections under 35 U.S.C. § 112, first paragraph, should be overturned.

ISSUE FOUR: Written description rejections under 35 U.S.C. § 112, first paragraph:

Claims 23, 26-28, and 31 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking adequate written description. In particular, the Examiner has asserted that the specification does not disclose nucleic acid molecules encoding a polypeptide at least 90% identical to the amino acid sequence of SEQ ID NO:22, or nucleic acids encoding biologically or immunologically active fragments of SEQ ID NO:22. The Office Action mailed March 25, 2003, asserted that "the skilled

artisan cannot envision all the detailed chemical structure of the claimed nucleic acid sequences" (page 7) and the "species specifically disclosed are not representative of the genus because the genus is highly variant" (page 8).

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met. (Footnotes omitted.)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

The Specification provides an adequate written description of the claimed "variants" and "fragments" of SEQ ID NO:22 and SEQ ID NO:101.

SEQ ID NO:22 and SEQ ID NO:101 are specifically disclosed in the application (see, for example, page 11, line 18 and page 12, line 18). Variants of SEQ ID NO:22 having 90% amino acid identity to SEQ ID NO:22 are described, for example, at page 11, lines 30-32. Polynucleotide variants having 90% polynucleotide sequence identity to the polynucleotide encoding SEQ ID NO:22 are described, for example, at page 12, lines 3-6. Polynucleotide variants having 90% polynucleotide

sequence identity to SEQ ID NO:101 are described, for example, at page 12, line 32 through page 13, line 2. Incyte clones in which the nucleic acids encoding the human HTMPN-22 were first identified and libraries from which those clones were isolated are described, for example, at page 73 (column 5 of Table 1) and page 97 (Table 4) of the specification. Chemical and structural features of HTMPN-22 are described, for example, at page 79 (Table 2) of the specification. Given SEQ ID NO:22 and SEQ ID NO:101, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:101 having 90% sequence identity to SEQ ID NO:101 or encoding amino acid sequences having 90% identity to SEQ ID NO:22.

In addition, the specification discloses examples of naturally occurring polynucleotide variants including allelic variants (page 15, lines 22-29), splice variants, species variants, or polymorphic variants, such as single nucleotide polymorphisms (SNPs) (page 23, lines 12-23). The specification discloses how to calculate the % identity between two sequences (see the specification at page 19, line 19 through page 20, line 3), allowing one of skill in the art to determine which naturally occurring sequences are encompassed by the claims. Accordingly, the specification provides an adequate written description of the recited variant polynucleotide sequences.

The Examiner has alleged that "it is not true that one could find in nature any and all possible changes within a given gene, and the specification has described not a single naturally occurring variant of SEQ ID NO:4. . . not a single sequence disclosed that is obtained from another biological species" (Office Action mailed November 3, 2003, page 21). Appellants are not claiming "any and all possible changes within a given gene." Appellants claim polynucleotides comprising a naturally occurring polynucleotide sequence at least 90% identical to SEQ ID NO:101 and polynucleotides encoding a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO:22.

The Examiner has questioned the truth of Appellants' statement in the Response filed June 24, 2003 that "one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:3 having 90% sequence identity to SEQ ID NO:22" (Office Action mailed November 3, 2003, page 21). The Examiner alleges that "[o]ne could certainly determine whether a protein that one had obtained from nature were 90% identical to SEQ ID NO:22, but that same person, handed a protein in a test

tube, would have no way of determining whether that protein were 'naturally occurring.' The same applies to the nucleic acid of SEQ ID NO:101" (Office Action mailed November 3, 2003, page 21).

Appellants note that sequence information is not provided in a vacuum. Identification of the source of the sequence will typically allow one to determine if it is naturally-occurring. Also, attempted deceit to hide the source will not preclude infringement.

Regarding the claimed sequences encoding biologically and immunologically active fragments of SEQ ID NO:22, the specification discloses a specific signature sequence, corresponding to a bromodomain, at residues A80-N140 (specification, page 79). The biological activities of bromodomain proteins as chromatin binding domains were well known in the art at the time of filing (see the Maruyama reference, page 6509, col. 1). Thus Appellants were clearly in possession of at least one biologically active fragment, explicitly identified in terms of its component amino acid sequence, at the time of filing. The Examiner has asserted that the specification "only teaches general computer based methods to determine regions of high immunogenicity" (Office Action mailed November 3, 2003, page 22). On the contrary, selection of immunogenic epitopes, such as regions at the C-terminus or hydrophilic regions, is described in the specification at page 70, lines 2-7. One of skill in the art would clearly find it trivial to select the C-terminal fragment of SEQ ID NO:22. Selection of hydrophobic regions of SEQ ID NO:22 would also require minimal effort given the ready availability of programs to analyze the hydrophobicity of amino acid sequences. Thus the specification also provides an adequate written description of the recited polynucleotide sequences encoding biologically and immunologically active fragments. An additional detailed listing of every possible such fragment is not required, and would only result in needlessly cluttering the specification.

A. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin Cana" or "mammalian insulin Cana," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of functional features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant phasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue

in the present application define polynucleotides in terms of chemical structure, rather than on functional characteristics. The "variant language" of independent claims 21 and 31 recites chemical structure to define the claimed genus:

> 21. An isolated polypeptide selected from the group consisting of . . . b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:22 . . .
>
> 31. An isolated polynucleotide selected from the group consisting of . . . b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:101 . . .

The Examiner attempts to distinguish the *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) cases from the instant case as "the claims in both those cases were limited to the naturally occurring sequences encoding particular proteins, which proteins are well known by their functions" and that "[i]n this case, Applicants claims required no such conserved function" (Office Action mailed November 3, 2003, page 23). In *Fiers*, the Examiner contends, "the person of ordinary skill in the art would immediately recognize that any and all species within the metes and bounds of 'A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide,' would encode proteins with *greater* than the 90% identity claimed by Applicants; the person of ordinary skill in the art would not expect to find that great an amount of variation within a single species, while still meeting the functional limitation of being a human fibroblast interferon-beta polypeptide" (Office Action mailed November 3, 2003, page 23, emphasis in original).

Appellants note first that the Examiner has provided only personal opinion to support this argument, without either evidence or sound scientific reasoning. Second, in the instant case the claimed species are described by not only their comprising "naturally-occurring" sequences but also by their percentage sequence identity with either SEQ ID NO:22 or SEQ ID NO:101. A structure is provided in the instant case by the recitation of a particular nucleotide or amino acid sequence, while it was not in the *Fiers* and *Lilly* claims. There is no recitation of the functional characteristics of the claimed polynucleotides. The polynucleotides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to

consider in a written description analysis of claims to nucleic acids. By failing to base the written description inquiry "on whatever is now claimed," the Examiner failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

B. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Board's attention is directed to the reference of record by Brenner et al. (*supra*). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to polynucleotides encoding Ring3 related bromodomain proteins related to the amino acid sequence of SEQ ID NO:22. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as Ring3 related bromodomain proteins and which have only 30% identity over at least 150 residues to SEQ ID NO:22. The present claims encompass naturally-occurring polynucleotide variants which have at least about 90% sequence identity to SEQ ID NO:101 or to polynucleotides encoding SEQ ID NO:22. This variation is far less than that of all potential Ring3 related bromodomain proteins related to SEQ ID NO:22, i.e., those Ring3 related bromodomain proteins having at least 30% identity over at least 150 residues to SEQ ID NO:22.

In response to this argument, the Examiner has contended that "[w]hile 90% identity is certainly sufficient to establish that two proteins are structurally similar and/or evolutionarily related, it is not predictive of function" (Office Action mailed November 3, 2003, page 25). As the claimed variants are

not described by their having the same "function" as SEQ ID NO:22 or SEQ ID NO:101, the Examiner's arguments are not relevant to the written description issue. Appellants respectfully note that the Brenner reference was not presented in order to demonstrate that the claimed polynucleotides all have a conserved function, but to demonstrate that the claimed genus is not highly variant, a point which the Examiner does not rebut.

C. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of May 29, 1998. Much has happened in the development of recombinant DNA technology in the 21 years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:22 and SEQ ID NO:101, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

D. Summary

The Examiner failed to base the written description inquiry "on whatever is now claimed." Consequently, the Examiner did not provide an appropriate analysis of the present claims and how they

differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:22 or SEQ ID NO:101. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids. In addition, the genus of DNA defined by the present claims is not "highly variant," as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Examiner.

For at least the reasons set forth above, the Specification provides an adequate written description of the claimed subject matter, and the written description rejections under 35 U.S.C. § 112, first paragraph, should be overturned.

(9) CONCLUSION

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, "like a nose of wax," to target rejections of claims to polypeptide and polynucleotide sequences where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specification as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

Appellants also respectfully submit that the Specification provides an adequate enabling disclosure and written description of the claimed subject matter, and the meaning of the claims is clear. Hence, the rejections based on the first paragraph of 35 U.S.C. §112 should be reversed.

Due to the urgency of this matter, including its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This brief is enclosed in triplicate

Respectfully submitted,

INCYTE CORPORATION

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APPENDIX - CLAIMS ON APPEAL

Claims 21 and 22, from which claims 23, 24, and 28 depend, are also listed here for reference.

21. (Withdrawn.) An isolated polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:22,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:22,

c) a biologically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:22, and

d) an immunologically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:22, wherein said immunologically active fragment generates an antibody that specifically binds to SEQ ID NO:22.

22. (Withdrawn.) An isolated polypeptide of claim 21 comprising the amino acid sequence of SEQ ID NO:22

23. An isolated polynucleotide encoding a polypeptide of claim 21.

24. An isolated polynucleotide encoding a polypeptide of claim 22.

25. An isolated polynucleotide of claim 24 comprising the polynucleotide sequence of SEQ ID NO:101.

26. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 23.

27. A cell transformed with a recombinant polynucleotide of claim 26.

28. A method of producing a polypeptide of claim 21, the method comprising:

a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 21, and

b) recovering the polypeptide so expressed.

29. A method of claim 28, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO:22.

31. An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:101,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:101,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).